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## CMC is more than a measure of corticospinal tract integrity in acute stroke patients

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### ABSTRACT

In healthy subjects, motor cortex activity and electromyographic (EMG) signals from contracting contralateral muscle show coherence in the beta (15–30 Hz) range. Corticomuscular coherence (CMC) is considered a sign of functional coupling between muscle and brain. Based on prior studies, CMC is altered in stroke, but functional significance of this finding has remained unclear. Here, we examined CMC in acute stroke patients and correlated the results with clinical outcome measures and corticospinal tract (CST) integrity estimated with diffusion tensor imaging (DTI). During isometric contraction of the extensor carpi radialis muscle, EMG and magnetoencephalographic oscillatory signals were recorded from 29 patients with paresis of the upper extremity due to ischemic stroke and 22 control subjects. CMC amplitudes and peak frequencies at 13–30 Hz were compared between the two groups. In the patients, the peak frequency in both the affected and the unaffected hemisphere was significantly ( $p < 0.01$ ) lower and the strength of CMC was significantly ( $p < 0.05$ ) weaker in the affected hemisphere compared to the control subjects. The strength of CMC in the patients correlated with the level of tactile sensitivity and clinical test results of hand function. In contrast, no correlation between measures of CST integrity and CMC was found. The results confirm the earlier findings that CMC is altered in acute stroke and demonstrate that CMC is bidirectional and not solely a measure of integrity of the efferent corticospinal tract.

### 1. Introduction

In stroke, the focal ischemic brain damage as well as disrupted cortical networks contribute to motor impairment. Function restoration is based on reorganization of these networks. In stroke patients with sensorimotor deficits, somatosensory representation areas have been shown to enlarge (Roiha et al., 2011), and additional cortical areas are recruited during a motor task (Ward et al., 2003). However, in patients with good recovery, sensorimotor cortical activity tends to focus towards initial contralateral patterns during recovery (Calautti et al.,

2001). Moreover, changes of cortical excitability are observed both in the ipsi- and contralesional hemispheres (Bütefisch et al., 2008; Nudo, 2007). Despite the advances in functional neuroimaging techniques, we still lack the precise knowledge of the neurophysiological mechanisms behind motor recovery (Calautti and Baron, 2003). To develop rehabilitation of motor impairment, we need to better learn the neurophysiological basis of motor recovery after stroke.

Previous studies using electroencephalography or magnetoencephalography (MEG) have shown that in the beta range (15–30 Hz), cortical oscillatory signals arising from the sensorimotor cortex are coherent

**Abbreviations:** AH, affected hemisphere; BB, Box and Block Test; CMC, corticomuscular coherence; CST, corticospinal tract; DTI, diffusion tensor imaging; EEG, electroencephalography; EMG, electromyography; FA, fractional anisotropy; FFT, a fast Fourier transform; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NHPT, Nine Hole Peg Test; NIHSS, National Institutes of Health Stroke Scale; PLIC, posterior limb of the internal capsule; UH, unaffected hemisphere.

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with electromyographic (EMG) signals during contralateral muscle contraction (Conway et al., 1995; Gross et al., 2000; Halliday et al., 1998; Salenius et al., 1997). The strength of corticomuscular coherence (CMC) has been shown to depend on the quality of movement: it is strongest during weak to moderate steady/static muscle contraction and abolishes during dynamic movement (Baker et al., 1997). Studies in patients with movement disorders, such as Parkinson's disease (Pollok et al., 2012; Salenius et al., 2002), essential tremor (Sharifi et al., 2017), spinocerebellar ataxia type 2 (Velázquez-Pérez et al., 2017) and amyotrophic lateral sclerosis (Proudfoot et al., 2018), have shown a disease-related decrease in the CMC amplitude (Proudfoot et al., 2018; Salenius et al., 2002; Sharifi et al., 2017; Velázquez-Pérez et al., 2017) as well as well-preserved CMC in the early phase of disease (Pollok et al., 2012). Only few CMC studies related to stroke (Braun et al., 2007; Fang et al., 2009; Graziadio et al., 2012; Larsen et al., 2017; Mima et al., 2001; Rossiter et al., 2013; von Carlowitz-Ghori et al., 2014) have been published, and they show variable alterations in amplitude and frequency of CMC.

In this study we measured CMC with MEG recordings of 29 acute ischemic stroke patients with motor impairment of the upper extremity. The aim was to evaluate how alterations of CMC after stroke are associated with the level of motor impairment and sensory deficits. We also aimed to evaluate how changes in CMC are related to measures of CST integrity.

## 2. Materials and methods

### 2.1. Subjects

29 patients (11 females, age 45–81 years, mean  $66 \pm 2$  years; all right-handed), with first-ever ischemic stroke in the middle cerebral artery territory, affecting upper limb motor function, and 22 healthy control subjects (11 females, age 42–78 years, mean  $59 \pm 2$  years; all right-handed) were enrolled into the study (Table 1). The patients were

recruited from the Department of Neurology, Helsinki University Hospital. Exclusion criteria were earlier neurological diseases, unstable general condition at the recruitment time, neurosurgical operations and mental disorders. All clinical tests, MEG recordings and magnetic resonance image (MRI) measurements with diffusion tensor imaging (DTI) were performed within 7 days from the onset of symptoms. Before the first measurement, all patients and control subjects participating in the study gave their written informed consent. The local Ethics Committee approved the study protocol.

### 2.2. Clinical testing

To determine the overall neurological deficits, a neurologist of the research team performed National Institutes of Health Stroke Scale (NIHSS). An occupational therapist tested the upper limb function with the Nine Hole Peg Test (NHPT; measured time to remove and replace nine pegs as fast as possible) and the Box and Block Test (BB; number of blocks moved in one minute over the partition from one compartment to another) to determine fine and gross hand dexterity (respectively). In NHPT, the defined maximum time, 180 s, was given if the task could not be performed at all or faster. Jamar dynamometer was used to measure grip strength. Tactile sensitivity was tested with von Frey monofilaments.

### 2.3. MEG and EMG recordings

Rhythmic cortical activity was recorded with a 306-channel neuro-magnetometer (Elekta Neuromag, Helsinki, Finland). The recordings were carried out in the magnetically shielded room of the BioMag Laboratory, Helsinki University Hospital. The data of the control subjects were recorded with an identical measurement device and set-up at Aalto University (Aalto Neuroimaging, MEG-Core). During the measurements, the subjects were seated in upright position with the head covered by a sensor array. With respect to the sensor array, the head

**Table 1**  
Patient characteristics.

Pat.	Gender	Age	AH	Cortex	Size	NIHSS	Jamar	BB	NHPT	VF
1	M	63	L	+	32	3	17	34	76	6,65
2	F	68	R	+	2	0	20	43	32	3,61
3	F	59	L	+	0	0	14	46	35	3,61
4	M	66	R	+	71	3	29	35	41	4,31
5	M	56	L	+	4	0	13	18	NA	3,61
6	M	45	R	+	84	7	62	64	21	3,61
7	F	58	R	+	32	2	9	17	180	4,31
8	F	66	L	+	8	3	0	0	180	NA
9	F	73	L	+	3	10	0	0	180	3,61
10	F	67	R	+	5	5	20	34	42	4,31
11	M	75	R	+	36	12	0	0	180	6,65
12	M	67	R	+	218	14	0	0	180	6,65
13	M	47	R	+	150	14	0	0	180	6,65
14	F	78	R	+	56	7	0	0	180	6,65
15	M	62	R	+	125	6	0	0	180	4,56
16	F	59	R	+	25	11	0	0	180	6,65
17	M	72	R	+	27	2	40	59	35	3,61
18	M	77	L	+	3	4	33	45	29	3,61
19	M	62	R	–	21	3	16	36	45	4,31
20	M	75	L	–	0	1	31	42	39	4,31
21	M	68	R	–	1	2	44	48	28	4,31
22	M	59	R	–	2	1	11	36	77	3,61
23	F	60	R	–	2	4	17	31	37	3,61
24	F	75	L	–	40	15	0	0	180	4,56
25	M	64	L	–	1	5	0	0	180	3,61
26	M	66	L	–	1	3	22	21	180	3,61
27	F	75	R	–	13	14	0	0	180	NA
28	M	66	R	–	3	5	20	31	155	4,31
29	M	81	R	–	1	5	0	0	180	NA

Age (years); AH, affected hemisphere; Cortex, cortical/subcortical lesion causing cortical damage; Size, lesion volume in  $\text{cm}^3$ ; NIHSS, National Institutes of Health Stroke Scale (0–42); Jamar, Jamar dynamometer (kg); BB, Box and Block Test; NHPT, Nine Hole Peg Test (s); VF, von Frey monofilaments (3,61 normal/reduced touch; 4,31 protective sensation reduced; 4,56 protective sensation not present; 6,65 tactile sense not measurable).

position was determined by measuring magnetic signals produced by indicator coils placed on the scalp. Rhythmic cortical activity was recorded during rest (eyes open/ eyes closed, three minutes each) and during extension of the wrist with moderate force. MEG signals were band-pass filtered through 0,03–330 Hz and digitized at 1000 Hz. During the task, the patients were asked to extend the wrists of both hands in separate sessions for a total of three minutes (one to two short breaks within contractions to avoid muscle fatigue). Despite the level of motor dysfunction, the patients were asked to try to perform and maintain the task in order to achieve moderate motor activity even if no wrist extension was observed. In both settings, EMG signals were measured with two bipolar surface electrodes placed over the extensor carpi radialis muscle. During the registration, two neurologists of the research team monitored EMG and MEG signals online. Alertness and performance of the patient was observed by a nurse inside the room. For the subjects, no visual feedback was used to monitor the force production. If any sign of fatigue was observed or if EMG signal started to change from the initial signal, the measurement was paused, and oral feedback was given to the patient in order to maintain a steady extension force. Each extension interval lasted for 60–90 s. After the measurement, EMG signal was analyzed off-line by a neurologist of the research team to confirm the strength of muscle activity.

## 2.4. MRI

MRI were taken from all patients using a 3 T MRI scanner (Philips Achieva 3 T, Philips Medical Systems, Best, The Netherlands) at Helsinki University Hospital, to determine the location and size of the lesion. DTI was used to assess the microstructure of the corticospinal tract (Basser et al., 1994). Voxelwise fractional anisotropy (FA) values were calculated from the robust tensor estimates (Leemans et al., 2009; Sairanen et al., 2018, 2017; Tax et al., 2015). A radiologist of the research team placed the volume-of-interest within the posterior limb of the internal capsule (PLIC), for both the affected (AH) and the unaffected (UH) hemispheres. Thereafter, asymmetry of PLIC integrity was calculated as follows: FA asymmetry = (FA(UH) – FA(AH))/(FA(UH) + FA(AH)), with positive FA asymmetry values indicating reduced FA in the affected PLIC (Stinear et al., 2007).

## 2.5. Data analysis

To suppress interfering noise, the MEG data were preprocessed with the temporal signal space separation method, implemented in Maxfilter software (Taulu and Simola, 2006), with a correlation window length of 16 s and a correlation limit of 0,98. By averaging over the measurement time the magnitudes of fast Fourier transforms (FFT) in half-overlapping sliding windows, the amplitude spectra of MEG signals during the task and rest (eyes open) and EMG signals during the task were calculated (Halliday et al., 1995). In order to assess the amplitudes of brain oscillations in the frequency range of 8–30 Hz, 2048-sample FFTs were used. CMC between MEG and rectified EMG signals was calculated at MEG sensor-level using the Welch's averaged periodogram method (Hanning 2048-point window; 2048 FFT size; 75% window overlap). When coherence exceeded the 95% confidence limit computed from the number of independent windows, it was considered significant (Halliday et al., 1995). Coherence spectra from the MEG channel showing the largest coherence value over the centroparietal region was selected for further analysis.

## 2.6. Statistical analysis

Statistical analyses were performed in SPSS Statistics (v 25; IBM) using one-way ANOVA and two-tailed *t*-test for pairwise comparisons. Correlations between coherence strength, FA asymmetry and clinical test results were calculated using Spearman's correlation coefficient. A *p*-value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Clinical test results

Among patients, all clinical test results of the impaired hand were significantly worse than those of the healthy hand ( $p < 0.01$ ; Table 1). 12 patients were not able to perform any of the motor tests of the impaired hand due to severity of the paresis. Stroke size ( $33 \pm 10 \text{ cm}^3$ ), location (cortical vs. subcortical) and NIHSS scores ( $6 \pm 1$ ) of the patients are presented in Table 1.

### 3.2. Spectrum of spontaneous brain activity

#### 3.2.1. During rest

Frequency and amplitude of spectral peaks of spontaneous brain activity during rest and isometric muscle contraction are presented in Tables 2a and 2b (significant differences in values between the patients and control subjects emboldened). Three major spectral peaks were detected over the Rolandic region; between 8 and 12 Hz, between 13 and 19 Hz and between 20 and 30 Hz both in the control subjects and in the patients. In the following we call the beta rhythm peaking between 13 and 19 Hz 'lower beta range' and the beta rhythm peaking between 20 and 30 Hz 'higher beta range'. In the lower beta range, during rest, the peak frequency was higher in the controls than in the patients (both AH and UH;  $p < 0.05$ ). In the higher beta range, the difference was observed only between the UH of the patients and the controls (Table 2a;  $p < 0.05$ ). During rest, no significant difference was found in the peak amplitudes between patients and control subjects (Table 2b).

#### 3.2.2. During task

During the task, the peak frequency was lower in the patients (both AH and UH) than in the controls ( $p < 0.01$ ), in the both beta frequency ranges (Table 2a). In the affected hemisphere, the peak amplitude in the lower beta range was significantly ( $p < 0.05$ ) higher in the patients than in the control subjects. No such difference was found for the UH nor in the higher beta range (Table 2b).

### 3.3. Corticomuscular coherence

CMC exceeding the 95% confidence limit was found in 17/22 (77%) control subjects. In patients, significant CMC was found in 17/28 (61%) in the AH and in 20/29 (69%) in the UH. In both the patients and the control subjects, the maximal CMC amplitude was observed in MEG channels over the contralateral Rolandic area with respect to the extended wrist, as reported in earlier studies (Baker et al., 2006; Conway et al., 1995; Mima et al., 2001).

Fig. 1 illustrates the grand-average of maximal CMC across the control subjects and the patients (both AH and UH). In the control subjects, the strongest coherence peak was  $0,12 \pm 0,02$  (hemispheres pooled); with no significant difference between the hemispheres (Fig. 2A). In the patients, the amplitude of the strongest CMC was  $0,07 \pm 0,01$  in the AH and  $0,08 \pm 0,01$  in the UH. No significant difference

**Table 2a**

Frequencies (Hz) of spectral peaks over the Rolandic area during rest (eyes open) and during the task.

	Ctrl		Patients			
	rest	task	rest		task	
			AH	UH	AH	UH
13–19 Hz	15.5 ± 0.3	16.5 ± 0.3	14.4 ± 0.3	14.7 ± 0.3	14.9 ± 0.3	14.5 ± 0.2
20–30 Hz	21.7 ± 0.3	22.6 ± 0.3	21.7 ± 0.4	20.8 ± 0.2	21.4 ± 0.2	21.3 ± 0.2

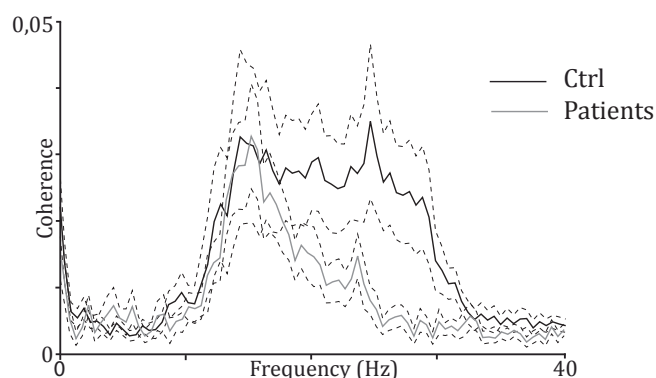
AH, affected hemisphere; UH, unaffected hemisphere; Ctrl, control subjects (hemispheres pooled).

**Table 2b**

Amplitudes (fT/cm $\sqrt{\text{Hz}}$ ) of spectral peaks over the Rolandic area during rest (eyes open) and during the task.

	Ctrl		Patients			
	rest	task	rest		task	
			AH	UH	AH	UH
13–19 Hz	13 $\pm$ 1	7 $\pm$ 1	15 $\pm$ 1	14 $\pm$ 1	10 $\pm$ 1	9 $\pm$ 1
20–30 Hz	9 $\pm$ 1	6 $\pm$ 0	10 $\pm$ 1	9 $\pm$ 1	6 $\pm$ 1	6 $\pm$ 0

AH, affected hemisphere; UH, unaffected hemisphere; Ctrl, control subjects (hemispheres pooled).



**Fig. 1.** Grand-average ( $\pm 95\%$  CI) of CMC across control subjects and patients (AH + UH) during contralateral wrist extension. AH, affected hemisphere; UH, unaffected hemisphere; Ctrl, control subjects (hemispheres pooled).

between the hemispheres in the strongest CMC amplitude was detected in the patients (Fig. 2B). Compared to the control subjects, the amplitude of the strongest CMC was significantly ( $p < 0.05$ ) weaker in the AH but not in the UH of the patients.

Fig. 3 shows individual CMC signals (from the channel showing the strongest CMC) in both the controls and the patients. In the control subjects, the strongest CMC for right and left wrist extension was observed at  $23 \pm 1$  Hz; no significant difference in the peak frequency was observed between the hemispheres. In the patients, the strongest CMC was observed at  $18 \pm 1$  Hz in the AH and at  $18 \pm 1$  Hz in the UH, with no significant difference between the hemispheres. The frequency of maximal CMC was significantly lower in the patients (both AH and UH) than in the control subjects ( $p < 0.01$ ).

### 3.4. Fractional anisotropy

FA values could be reliably defined in 22/29 of the patients. 7 datasets were rejected due to defective recordings or severe motion artifacts. Mean PLIC FA values were  $0.67 \pm 0.01$  in the AH and  $0.69 \pm 0.01$  in the UH with no significant difference between the hemispheres. The mean FA asymmetry was 0.02 (range  $-0.11$ – $0.17$ ).

### 3.5. Correlation analysis

CMC peak amplitudes of the AH in the whole beta range correlated significantly with the results of Jamar dynamometer ( $r_s = 0.4$ ,  $p < 0.05$ ), BB ( $r_s = 0.5$ ,  $p < 0.01$ ), NHPT ( $r_s = -0.5$ ,  $p < 0.01$ ) and von Frey monofilaments test results ( $r_s = -0.4$ ,  $p < 0.05$ ) of the impaired hand; the stronger the CMC amplitude, the better the hand motor function, strength and tactile sensitivity. There was no significant correlation between NIHSS, size of the lesion and CMC peak amplitudes of the AH. No correlation was detected between CMC peak amplitudes of the UH and size of the lesion, NIHSS nor clinical test results of the healthy hand.

FA asymmetry values correlated significantly with NIHSS and all clinical test results of the impaired hand (NIHSS ( $r_s = 0.6$ ,  $p < 0.01$ ), Jamar dynamometer ( $r_s = -0.5$ ,  $p < 0.05$ ), BB ( $r_s = -0.5$ ,  $p < 0.05$ ), NHPT ( $r_s = 0.6$ ,  $p < 0.01$ )); the larger the FA asymmetry (reduced FA in the AH) the worse the overall neurological outcome and the impaired hand motor function. In contrast, no significant correlation was detected between AH peak CMC amplitudes, von Frey monofilaments test results and FA asymmetry values.

## 4. Discussion

The present study shows that CMC is altered in acute stroke patients. In this study, the amplitude of maximal CMC is significantly weaker, and it occurs at significantly lower frequencies than in healthy control subjects.

The strength of maximal CMC is associated with clinical test results of hand function; the stronger the CMC amplitude the better the impaired hand strength, dexterity and tactile sensitivity. To our knowledge, for the first time, we combine CMC with measures of CST integrity and importantly, show no correlation between these two.

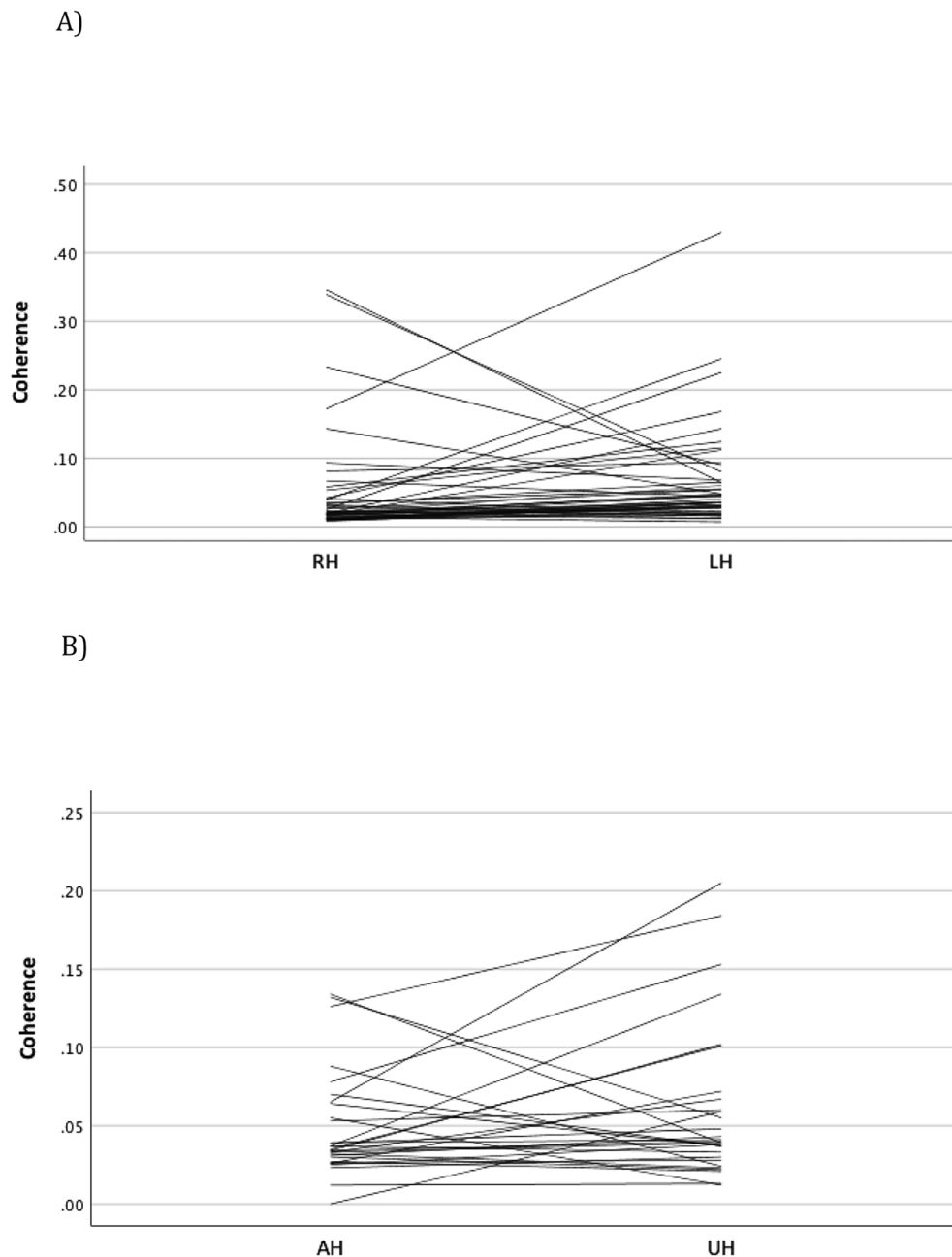
### 4.1. Neurophysiological basis of CMC and corticospinal tract integrity

The functional role of CMC remains unclear. Although CMC has previously been thought to reflect the cortical drive to muscles (Salenius et al., 1997), previous studies have indicated that ascending sensory signals also contribute to CMC (Baker et al., 2006; Fisher et al., 2002; Lim et al., 2014; Mima et al., 2001; Pohja et al., 2002; Riddle and Baker, 2005; Witham et al., 2011).

CMC has been used in clinical settings as a measure of CST integrity. This study is, to our knowledge, among the first ones to investigate both CST integrity and CMC in the same patients. The results show no significant correlation between FA asymmetry values and CMC peak amplitude strength supporting the hypothesis that CMC is more than a measure of anatomical integrity in the corticospinal tract. An earlier study showed that stronger coherence values were associated with better motor performance, indicating that, as a stabilizer of corticospinal communication, beta-range corticomuscular coherence may have an important role in successful sensorimotor integration (Witte et al. 2007). In accordance, the present study shows that the strength of CMC correlates both with motor performance (NHPT, BB, Jamar) and the level of tactile sensitivity; the weaker the CMC, the poorer the hand motor function and tactile sensitivity. On the other hand, some of the patients who could not perceive touch sensation with von Frey filaments, showed significant CMC. Hence, the results indicate that although CMC is a bidirectional measure, ascending tactile input is not a prerequisite for CMC. Taken together, these results suggest that CMC reflects a complex bidirectional system that tunes sensorimotor interaction. The recordings of the present study were performed within a week of the stroke onset. It is possible that at such an early phase of stroke, some of the defects of neuronal networks are observable in functional measures rather than in anatomical connections, explaining the deviating results between DTI and CMC measurements.

A previous study (Graziadio et al., 2012) with eleven stroke patients, medium 6.5 years after stroke, showed that changes in corticospinal level after unilateral stroke occurred bilaterally, both in the lesioned and in the non-lesioned corticospinal systems. Recovery of the patients correlated with the degree of symmetry on cortical and spinomuscular level and CMC. Respectively, changes in CMC after acute stroke in our study were seen not only in the affected hemisphere but also in the unaffected hemisphere. At the acute phase, there was no significant difference between hemispheres in CMC peak frequencies nor in CMC peak frequency amplitudes. Our findings support the previous results that changes in corticospinal system after stroke happen bilaterally. Follow-up studies are needed to find out how these changes correlate with clinical findings during recovery of the patients.





**Fig. 2.** A) Peak amplitudes of CMC in the beta frequency range in the right (RH) and in the left (LH) hemispheres in control subjects. B) Peak amplitudes of CMC in the beta frequency range in the affected (AH) and in the unaffected (UH) hemispheres in patients.

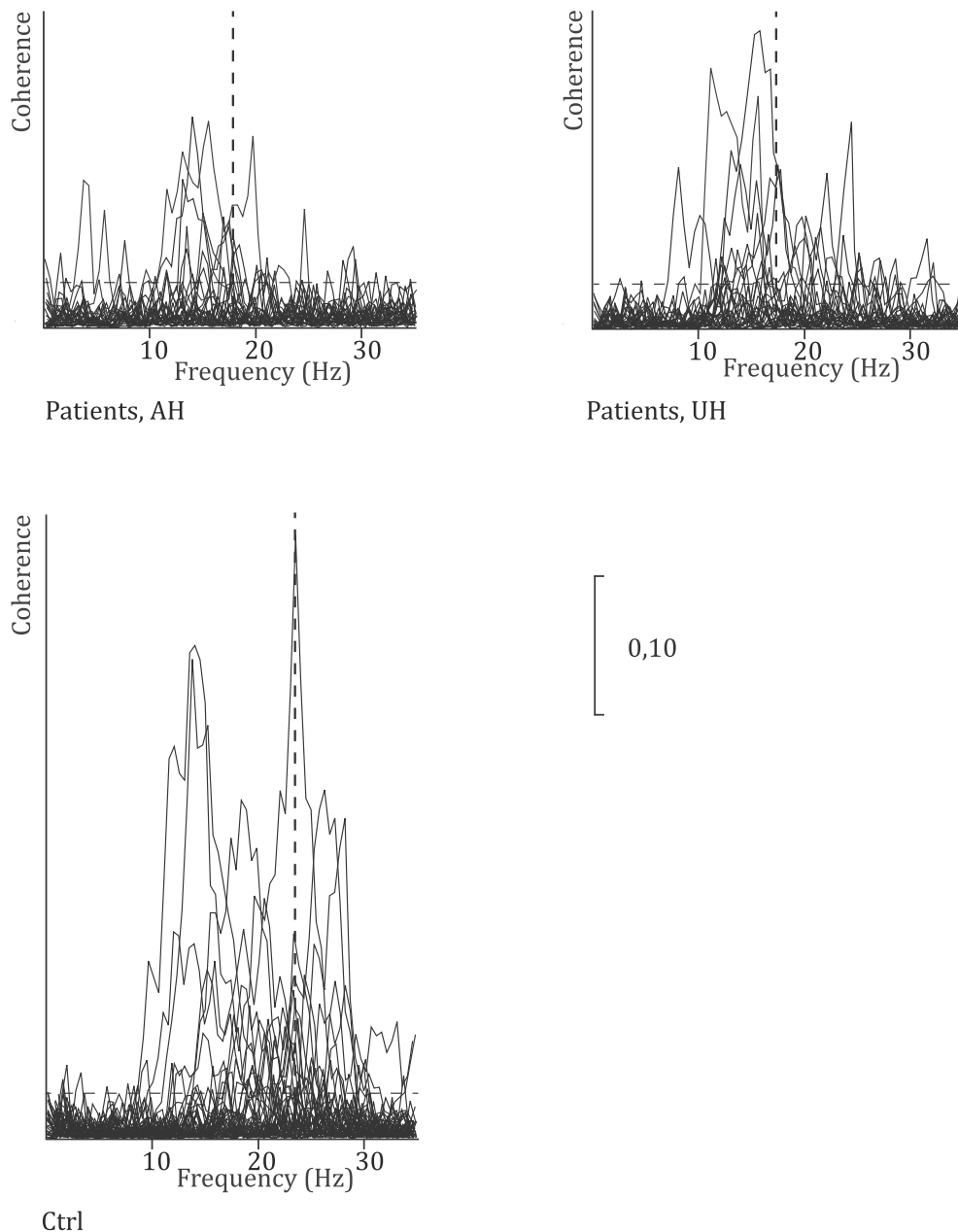
#### 4.2. Frequency and strength of CMC

Several earlier EEG and MEG studies have indicated that there are at least two distinct Rolandic beta rhythms, which differ in their frequency, generator areas and functional role. (Hall et al., 2011; Jurkiewicz et al., 2006; Pfurtscheller et al., 1997). In line with these findings, we showed in our previous stroke study (Laaksonen et al., 2012) that rhythmic activity in the lower and higher beta range are modulated differently to tactile stimulation.

In the present study, the maximal CMC in the patients was detected at significantly slower frequencies than in healthy controls. Our findings are similar with results from earlier studies showing strongest CMC in the patients at significantly lower frequencies than in healthy controls both in acute (Larsen et al., 2017; von Carlowitz-Ghori et al., 2014) and subacute stroke (Larsen et al., 2017). The results have been interpreted

as slowing of CMC from higher to lower beta frequencies (von Carlowitz-Ghori et al., 2014). An earlier study showed that CMC frequency is dependent on motor task quality; CMC occurred at lower beta frequencies often during a maintained motor contraction task, whereas CMC was detected at higher frequency levels (15–30 Hz) during tasks demanding high precision (Kristeva-Feige et al., 2002). Thus, it may be that CMC frequency of the patients is not just slowed down but rather lacks coherent signals in the higher beta range. However, this remains speculative and needs further investigations.

There are only few studies comparing CMC strength in acute stroke with healthy subjects. Larsen et al. (2017) showed that, compared with control subjects, the amplitude of maximal CMC in the patients was reduced, whereas von Carlowitz-Ghori et al. (2014) showed no significant difference in CMC amplitude between controls and AH or UH of the patients in the acute stroke. In the present study, the amplitude of



**Fig. 3.** Peak amplitude CMC curves in control subjects and patients. Mean frequency of maximal CMC is shown in vertical dashed lines. Horizontal dashed lines mark the 5% significance value for the observed coherence. AH, affected hemisphere; UH, unaffected hemisphere; Ctrl, control subjects (hemispheres pooled).

maximal CMC in the AH of the patients and the peak frequency occurred at significantly slower frequencies compared to the control subjects. As frequency of CMC has been shown to depend on the quality of motor task (Kristeva-Feige et al., 2002), the observed differences in CMC peak amplitudes could partly be explained with different strategies of the patients trying to accomplish the given motor task.

#### 4.3. CMC and resting state oscillations

In line with previous findings (von Carlowitz-Ghori et al., 2014), we did not observe any changes in the frequency nor amplitude of resting-state beta oscillations in our patients. Indeed, a dissociation between cortical oscillations and CMC has already been shown earlier in healthy subjects: doubling of cortical 20-Hz activity by administering diazepam did not change the strength of CMC (Baker and Baker, 2003). In line, although the modulation of 20-Hz oscillations to tactile or proprioceptive stimulation has shown to be altered after stroke, no changes in

resting-state beta oscillations were observed (Laaksonen et al., 2012; Parkkonen et al., 2018). Hence, changes in resting state oscillations are not sufficient to explain the observed slowing of CMC peak frequency.

#### 4.4. Sources of error

Compared with the patients with milder upper limb paresis, patients with greater motor dysfunction would have to put much more effort to achieve higher force levels. According to a previous study (Johnson et al., 2011) the level of attention in a motor task alters significantly CMC. As the degree of paresis of the upper extremity varied among the patients, we considered that equal amount of attention rather than similar muscle force would give better insight into the central-peripheral communication in stroke patients. However, we are aware of the possible shortcoming in interpretation of the results due to varying degree of paralysis of our patients.

#### 4.5. Conclusion

In the present study, we show that CMC is a complex bidirectional measure that is dependent on both afferent and efferent input: the level of tactile sensitivity and motor strength of the impaired hand correlates with CMC values but on the other hand, significant CMC is also present in patients with sensation loss. At the same time, fractional anisotropy values do not correlate with CMC values, which demonstrates that CMC is more than a measure of CST anatomical integrity.

In this study, the amplitude of maximal CMC is reduced and occurs at lower frequencies compared with healthy subjects. Follow-up studies are needed in order to find out how changes in CMC correlate with motor improvement and if CMC could be used in the future as a prognostic tool for stroke patients.

#### CRediT authorship contribution statement

**R. Aikio:** Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **K. Laaksonen:** Conceptualization, Methodology, Investigation, Validation, Writing - review & editing. **V. Sairanen:** Software, Writing - review & editing. **E. Parkkonen:** Investigation, Data curation. **A. Abou Elseoud:** Formal analysis. **J. Kujala:** Software. **N. Forss:** Conceptualization, Methodology, Supervision, Funding acquisition.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### References

- Baker, M.R., Baker, S.N., 2003. The effect of diazepam on motor cortical oscillations and corticomuscular coherence studied in man. *J. Physiol.* 546 (3), 931–942. <https://doi.org/10.1113/jphysiol.2002.029553>.
- Baker, S.N., Chiu, M., Fetz, E.E., 2006. Afferent encoding of central oscillations in the monkey arm. *J. Neurophysiol.* 95 (6), 3904–3910. <https://doi.org/10.1152/jn.01106.2005>.
- Baker, S.N., Olivier, E., Lemon, R.N., 1997. Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. *J. Physiol.* 501 <https://doi.org/10.1111/j.1469-7793.1997.225bo.x>.
- Basser, P.J., Mattiello, J., Lebihan, D., 1994. Estimation of the Effective Self-Diffusion Tensor from the NMR Spin Echo. *J. Magn. Reson., Ser B* 103 (3), 247–254. <https://doi.org/10.1006/jmrb.1994.1037>.
- Braun, C., Staudt, M., Schmitt, C., Preissl, H., Birbaumer, N., Gerloff, C., 2007. Crossed cortico-spinal motor control after capsular stroke. *Eur. J. Neurosci.* 25 <https://doi.org/10.1111/j.1460-9568.2007.05526.x>.
- Bütefisch, C.M., Wepfling, M., Netz, J., Seitz, R.J., Hömberg, V., 2008. Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. *Neurorehabil. Neural Repair* 22 (1), 4–21. <https://doi.org/10.1177/1545968307301769>.
- Calautti, C., Baron, J.-C., 2003. Functional neuroimaging studies of motor recovery after stroke in adults: A review. *Stroke* 34 (6), 1553–1566. <https://doi.org/10.1161/01.STR.0000071761.36075.A6>.
- Calautti, C., Leroy, F., Guineestre, J.-Y., Marié, R.-M., Baron, J.-C., 2001. Sequential activation brain mapping after subcortical stroke: Changes in hemispheric balance and recovery. *NeuroReport* 12 (18), 3883–3886. <https://doi.org/10.1097/00001756-200112210-00005>.
- Conway, B.A., Halliday, D.M., Farmer, S.F., Shahani, U., Maas, P., Weir, A.I., Rosenberg, J.R., 1995. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. *J. Physiol.* 489 <https://doi.org/10.1113/jphysiol.1995.sp021104>.
- Fang, Y., Daly, J.J., Sun, J., Hovorat, K., Fredrickson, E., Pundik, S., Sahgal, V., Yue, G.H., 2009. Functional corticomuscular connection during reaching is weakened following stroke. *Clin. Neurophysiol.* 120 (5), 994–1002. <https://doi.org/10.1016/j.clinph.2009.02.173>.
- Fisher, R.J., Galea, M.P., Brown, P., Lemon, R.N., 2002. Digital nerve anaesthesia decreases EMG-EMG coherence in a human precision grip task. *Exp. Brain Res.* 145 (2), 207–214. <https://doi.org/10.1007/s00221-002-1113-x>.
- Graziadio, S., Tomasevic, L., Assenza, G., Tecchio, F., Eyre, J.A., 2012. The myth of the “unaffected” side after unilateral stroke: Is reorganisation of the non-infarcted corticospinal system to re-establish balance the price for recovery? *Exp. Neurol.* 238 (2), 168–175. <https://doi.org/10.1016/j.expneurol.2012.08.031>.
- Gross, J., Tass, P.A., Salenius, S., Hari, R., Freund, H.-J., Schnitzler, A., 2000. Cortico-muscular synchronization during isometric muscle contraction in humans as revealed by magnetoencephalography. *J. Physiol.* 527 (3), 623–631. <https://doi.org/10.1111/tjp.2000.527.issue-310.1111/j.1469-7793.2000.00623.x>.
- Hall, S.D., Stanford, I.M., Yamawaki, N., McAllister, C.J., Rönnqvist, K.C., Woodhall, G. L., Furlong, P.L., 2011. The role of GABAergic modulation in motor function related neuronal network activity. *Neuroimage* 56 (3), 1506–1510. <https://doi.org/10.1016/j.neuroimage.2011.02.025>.
- Halliday, D.M., Conway, B.A., Farmer, S.F., Rosenberg, J.R., 1998. Using electroencephalography to study functional coupling between cortical activity and electromyograms during voluntary contractions in humans. *Neurosci. Lett.* 241 (1), 5–8. [https://doi.org/10.1016/S0304-3940\(97\)00964-6](https://doi.org/10.1016/S0304-3940(97)00964-6).
- Halliday, D.M., Rosenberg, J.R., Amjad, A.M., Breeze, P., Conway, B.A., Farmer, S.F., 1995. A framework for the analysis of mixed time series/point process data-Theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog. Biophys. Mol. Biol.* [https://doi.org/10.1016/S0079-6107\(96\)00009-0](https://doi.org/10.1016/S0079-6107(96)00009-0).
- Johnson, A.N., Wheaton, L.A., Shinohara, M., 2011. Attenuation of corticomuscular coherence with additional motor or non-motor task. *Clin. Neurophysiol.* 122 (2), 356–363. <https://doi.org/10.1016/j.clinph.2010.06.021>.
- Jurkiewicz, M.T., Gaetz, W.C., Bostan, A.C., Cheyne, D., 2006. Post-movement beta rebound is generated in motor cortex: Evidence from neuromagnetic recordings. *Neuroimage* 32 (3), 1281–1289. <https://doi.org/10.1016/j.neuroimage.2006.06.005>.
- Kristeva-Feige, R., Fritsch, C., Timmer, J., Lücking, C.-H., 2002. Effects of attention and precision of exerted force on beta range EEG-EMG synchronization during a maintained motor contraction task. *Clin. Neurophysiol.* 113 (1), 124–131. [https://doi.org/10.1016/S1388-2457\(01\)00722-2](https://doi.org/10.1016/S1388-2457(01)00722-2).
- Laaksonen, K., Kirveskari, E., Mäkelä, J.P., Kaste, M., Mustanoja, S., Nummenmaa, L., Tatlisumak, T., Forss, N., 2012. Effect of afferent input on motor cortex excitability during stroke recovery. *Clin. Neurophysiol.* 123 (12), 2429–2436. <https://doi.org/10.1016/j.clinph.2012.05.017>.
- Larsen, L.H., Zibbrandtsen, I.C., Wienecke, T., Kjaer, T.W., Christensen, M.S., Nielsen, J.B., Langberg, H., 2017. Corticomuscular coherence in the acute and subacute phase after stroke. *Clin. Neurophysiol.* 128 (11), 2217–2226. <https://doi.org/10.1016/j.clinph.2017.08.033>.
- Leemans, A., Jeurissen, B., Sijbers, J., Jones, D.K., 2009. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. *Proceedings of the International Society for Magnetic Resonance in Medicine*.
- Lim, M., Kim, J.S., Kim, M., Chung, C.K., 2014. Ascending beta oscillation from finger muscle to sensorimotor cortex contributes to enhanced steady-state isometric contraction in humans. *Clin. Neurophysiol.* 125 (10), 2036–2045. <https://doi.org/10.1016/j.clinph.2014.02.006>.
- Mima, T., Toma, K., Koshy, B., Hallett, M., 2001. Coherence between cortical and muscular activities after subcortical stroke. *Stroke* 32 (11), 2597–2601. <https://doi.org/10.1161/hs1101.098764>.
- Nudo, R.J., 2007. Postinfarct cortical plasticity and behavioral recovery. In: *Stroke*. <https://doi.org/10.1161/01.STR.0000247943.12887.d2>.
- Parkkonen, E., Laaksonen, K., Parkkonen, L., Forss, N., 2018. Recovery of the 20Hz rebound to tactile and proprioceptive stimulation after stroke. *Neural Plast.* 2018 <https://doi.org/10.1155/2018/7395798>.
- Pfurtscheller, G., Stancák, A., Edlinger, G., 1997. On the existence of different types of central beta rhythms below 30 Hz. *Electroencephalogr. Clin. Neurophysiol.* 102 (4), 316–325. [https://doi.org/10.1016/S0013-4694\(96\)96612-2](https://doi.org/10.1016/S0013-4694(96)96612-2).
- Pohja, M., Salenius, S., Hari, R., 2002. Cortico-muscular coupling in a human subject with mirror movements - A magnetoencephalographic study. *Neurosci. Lett.* 327 (3), 185–188. [https://doi.org/10.1016/S0304-3940\(02\)00426-3](https://doi.org/10.1016/S0304-3940(02)00426-3).
- Pollok, B., Krause, V., Martsch, W., Wach, C., Schnitzler, A., Südmeyer, M., 2012. Motor-cortical oscillations in early stages of Parkinson's disease. *J. Physiol.* 590 <https://doi.org/10.1113/jphysiol.2012.231316>.
- Proudfoot, M., van Ede, F., Quinn, A., Colclough, G.L., Wu, J., Talbot, K., Benatar, M., Woolrich, M.W., Nobre, A.C., Turner, M.R., 2018. Impaired corticomuscular and interhemispheric cortical beta oscillation coupling in amyotrophic lateral sclerosis. *Clin. Neurophysiol.* 129 (7), 1479–1489. <https://doi.org/10.1016/j.clinph.2018.03.019>.
- Riddle, C.N., Baker, S.N., 2005. Manipulation of peripheral neural feedback loops alters human corticomuscular coherence. *J. Physiol.* 566 <https://doi.org/10.1113/jphysiol.2005.089607>.
- Roiha, K., Kirveskari, E., Kaste, M., Mustanoja, S., Mäkelä, J.P., Salonen, O., Tatlisumak, T., Forss, N., 2011. Reorganization of the primary somatosensory cortex during stroke recovery. *Clin. Neurophysiol.* 122 (2), 339–345. <https://doi.org/10.1016/j.clinph.2010.06.032>.
- Rossiter, H.E., Eaves, C., Davis, E., Boudrias, M.-H., Park, C.-H., Farmer, S., Barnes, G., Litvak, V., Ward, N.S., 2013. Changes in the location of cortico-muscular coherence following stroke. *NeuroImage Clin.* 2, 50–55. <https://doi.org/10.1016/j.nicl.2012.11.002>.
- Sairanen, V., Kuusela, L., Sipilä, O., Savolainen, S., Vanhatalo, S., 2017. A novel measure of reliability in Diffusion Tensor Imaging after data rejections due to subject motion. *Neuroimage* 147, 57–65. <https://doi.org/10.1016/j.neuroimage.2016.11.061>.



- Sairanen, V., Leemans, A., Tax, C.M.W., 2018. Fast and accurate Slicewise Outlier Detection (SOLID) with informed model estimation for diffusion MRI data. *Neuroimage* 181, 331–346. <https://doi.org/10.1016/j.neuroimage.2018.07.003>.
- Salenius, S., Avikainen, S., Kaakkola, S., Hari, R., Brown, P., 2002. Defective cortical drive to muscle in Parkinson's disease and its improvement with levodopa. *Brain* 125 (3), 491–500. <https://doi.org/10.1093/brain/awf042>.
- Salenius, S., Portin, K., Kajola, M., Salmelin, R., Hari, R., 1997. Cortical control of human motoneuron firing during isometric contraction. *J. Neurophysiol.* 77 (6), 3401–3405. <https://doi.org/10.1152/jn.1997.77.6.3401>.
- Sharifi, S., Luft, F., Verhagen, R., Heida, T., Speelman, J.D., Bour, L.J., van Rootselaar, A.-F., 2017. Intermittent cortical involvement in the preservation of tremor in essential tremor. *J. Neurophysiol.* 118 (5), 2628–2635. <https://doi.org/10.1152/jn.00848.2016>.
- Stinear, C.M., Barber, P.A., Smale, P.R., Coxon, J.P., Fleming, M.K., Winston, D.B., 2007. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* 130 (1), 170–180. <https://doi.org/10.1093/brain/awl333>.
- Taulu, S., Simola, J., 2006. Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Phys. Med. Biol.* 51 (7), 1759–1768. <https://doi.org/10.1088/0031-9155/51/7/008>.
- Tax, C.M.W., Otte, W.M., Viergever, M.A., Dijkhuizen, R.M., Leemans, A., 2015. REKINDLE: Robust Extraction of Kurtosis INDices with Linear Estimation. *Magn. Reson. Med.* 73 (2), 794–808. <https://doi.org/10.1002/mrm.25165>.
- Velázquez-Pérez, L., Tünnnerhoff, J., Rodríguez-Labrada, R., Torres-Vega, R., Ruiz-Gonzalez, Y., Belardinelli, P., Medrano-Montero, J., Canales-Ochoa, N., González-Zaldívar, Y., Vazquez-Mojena, Y., Auburger, G., Ziemann, U., 2017. Early corticospinal tract damage in prodromal SCA2 revealed by EEG-EMG and EMG-EMG coherence. *Clin. Neurophysiol.* 128 (12), 2493–2502. <https://doi.org/10.1016/j.clinph.2017.10.009>.
- von Carlowitz-Ghori, K., Bayraktaroglu, Z., Hohlefeld, F.U., Losch, F., Curio, G., Nikulin, V.V., 2014. Corticomuscular coherence in acute and chronic stroke. *Clin. Neurophysiol.* 125 (6), 1182–1191. <https://doi.org/10.1016/j.clinph.2013.11.006>.
- Ward, N.S., Brown, M.M., Thompson, A.J., Frackowiak, R.S.J., 2003. Neural correlates of motor recovery after stroke: A longitudinal fMRI study. *Brain* 126. <https://doi.org/10.1093/brain/awg245>.
- Witham, C.L., Riddle, C.N., Baker, M.R., Baker, S.N., 2011. Contributions of descending and ascending pathways to corticomuscular coherence in humans. *J. Physiol.* 589. <https://doi.org/10.1113/jphysiol.2011.211045>.
- Witte, M., Patino, L., Andrykiewicz, A., Hepp-Reymond, M.C., Kristeva, R., 2007. Modulation of human corticomuscular beta-range coherence with low-level static forces. *Eur. J. Neurosci.* 26. <https://doi.org/10.1111/j.1460-9568.2007.05942.x>.